# Detailed methods for *Optimal targeting of seasonal influenza vaccination toward younger ages is robust to parameter uncertainty*

Martial L. Ndeffo Mbah[*†] Jan Medlock[‡§]
Lauren Ancel Meyers[¶] Alison P. Galvani[*]
Jeffrey P. Townsend[‖]

We extended the age-structured SEIR (susceptible, latent, infectious, recovered) model of Medlock & Galvani [7] to include two levels of risk for complications due to influenza infection and parametrized this model using epidemiological data from seasonal influenza.

Here we detail the model construction and parametrization.

## S1.1 Mathematical Model

### S1.1.1 Transmission Model

For modeling influenza transmission in the United States, we divide the population into the 17 age groups for ages 0, 1–4, 5–9, 10–14, 15–19, 20–24,

[*]Department of Epidemiology and Public Health, Yale University School of Medicine, 135 College Street, New Haven, CT 06520

[†]Corresponding author. Email: martial.ndeffo-mbah@yale.edu

[‡]Department of Mathematical Sciences, Clemson University, Box 340975, Clemson, SC 29634

[§]Department of Biomedical Sciences, Oregon State University, 105 Magruder Hall, Corvallis, OR 97331

[¶]Section of integrative biology, The University of Texas, Austin, TX, USA

[‖]Department of Ecology and Evolutionary Biology, Yale University, New Haven, CT, USA

25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75+. The numbers of people in each age group were parametrized using the estimated US 2010 population [14]. Within each age, we further divide the population into low risk and high risk for influenza complications, with high risk being identified by existing medical conditions such as asthma, heart disease, and pregnancy. In our model, the only impact of being in the high-risk group was an increased risk of averse outcomes, death and hospitalization, from influenza infection.

Each of the age–risk groups is then stratified by infection status. Let $S_{\mathrm{LU}a}(t)$, $E_{\mathrm{LU}a}(t)$, $I_{\mathrm{LU}a}(t)$, and $R_{\mathrm{LU}a}(t)$ be the respective numbers of unvaccinated low-risk susceptible, latent, infectious, and recovered people in age groups $a = 1, 2, \ldots, 17$. Let $S_{\mathrm{HU}a}(t)$, $E_{\mathrm{HU}a}(t)$, $I_{\mathrm{HU}a}(t)$, and $R_{\mathrm{HU}a}(t)$ be defined similarly, but for unvaccinated high-risk people. Now, let $S_{\mathrm{LV}a}(t)$, $E_{\mathrm{LV}a}(t)$, $I_{\mathrm{LV}a}(t)$, $R_{\mathrm{LV}a}(t)$, $S_{\mathrm{HV}a}(t)$, $E_{\mathrm{HV}a}(t)$, $I_{\mathrm{HV}a}(t)$, $R_{\mathrm{HV}a}(t)$ be defined similarly for vaccinated people.

The infection dynamics are described by the differential equations

$$
\begin{aligned}
\frac{\mathrm{d}S_{\mathrm{LU}a}}{\mathrm{d}t} &= -\lambda_a S_{\mathrm{LU}a}, \\
\frac{\mathrm{d}E_{\mathrm{LU}a}}{\mathrm{d}t} &= \lambda_a S_{\mathrm{LU}a} - \tau_a E_{\mathrm{LU}a}, \\
\frac{\mathrm{d}I_{\mathrm{LU}a}}{\mathrm{d}t} &= \tau_a E_{\mathrm{LU}a} - (\gamma_a + \nu_{\mathrm{LU}a}) I_{\mathrm{LU}a}, \\
\frac{\mathrm{d}R_{\mathrm{LU}a}}{\mathrm{d}t} &= \gamma_a I_{\mathrm{LU}a}, \\
\frac{\mathrm{d}S_{\mathrm{HU}a}}{\mathrm{d}t} &= -\lambda_a S_{\mathrm{HU}a}, \\
\frac{\mathrm{d}E_{\mathrm{HU}a}}{\mathrm{d}t} &= \lambda_a S_{\mathrm{HU}a} - \tau_a E_{\mathrm{HU}a}, \\
\frac{\mathrm{d}I_{\mathrm{HU}a}}{\mathrm{d}t} &= \tau_a E_{\mathrm{HU}a} - (\gamma_a + \nu_{\mathrm{HU}a}) I_{\mathrm{HU}a}, \\
\frac{\mathrm{d}R_{\mathrm{HU}a}}{\mathrm{d}t} &= \gamma_a I_{\mathrm{HU}a}, \\
\frac{\mathrm{d}S_{\mathrm{LV}a}}{\mathrm{d}t} &= -(1-\epsilon_a)\lambda_a S_{\mathrm{LV}a}, \\
\frac{\mathrm{d}E_{\mathrm{LV}a}}{\mathrm{d}t} &= (1-\epsilon_a)\lambda_a S_{\mathrm{LV}a} - \tau_a E_{\mathrm{LV}a}, \\
\frac{\mathrm{d}I_{\mathrm{LV}a}}{\mathrm{d}t} &= \tau_a E_{\mathrm{LV}a} - (\gamma_a + \nu_{\mathrm{LV}a}) I_{\mathrm{LV}a}, \\
\frac{\mathrm{d}R_{\mathrm{LV}a}}{\mathrm{d}t} &= \gamma_a I_{\mathrm{LV}a}, \\
\frac{\mathrm{d}S_{\mathrm{HV}a}}{\mathrm{d}t} &= -(1-\epsilon_a)\lambda_a S_{\mathrm{HV}a}, \\
\frac{\mathrm{d}E_{\mathrm{HV}a}}{\mathrm{d}t} &= (1-\epsilon_a)\lambda_a S_{\mathrm{HV}a} - \tau_a E_{\mathrm{HV}a}, \\
\frac{\mathrm{d}I_{\mathrm{HV}a}}{\mathrm{d}t} &= \tau_a E_{\mathrm{HV}a} - (\gamma_a + \nu_{\mathrm{HV}a}) I_{\mathrm{HV}a}, \\
\frac{\mathrm{d}R_{\mathrm{HV}a}}{\mathrm{d}t} &= \gamma_a I_{\mathrm{HV}a}
\end{aligned}
\tag{S1.1}
$$

for $a = 1, \ldots, 17$. The progression rate to infectiousness for people in age group $a$ is $\tau_a$ and the recovery rate is $\gamma_a$. The influenza-induced death rates for people in age group $a$ are $\nu_{\mathrm{LU}a}$, $\nu_{\mathrm{HU}a}$, $\nu_{\mathrm{LV}a}$, and $\nu_{\mathrm{HV}a}$, respectively, for unvaccinated low-risk, unvaccinated high-risk, vaccinated low-risk, and vac-

cinated high-risk people. The vaccine efficacy in age group $a$ is $\epsilon_a$. The force of infection is given by

$$\begin{aligned}\lambda_a &= \sum_{\alpha=1}^{17} \frac{\beta\sigma_a\phi_{a\alpha}\left(I_{\mathrm{LU}\alpha} + I_{\mathrm{HU}\alpha} + I_{\mathrm{LV}\alpha} + I_{\mathrm{HV}\alpha}\right)}{N} \\ &= \frac{\beta\sigma_a}{N}\sum_{\alpha=1}^{17}\phi_{a\alpha}\left(I_{\mathrm{LU}\alpha} + I_{\mathrm{HU}\alpha} + I_{\mathrm{LV}\alpha} + I_{\mathrm{HV}\alpha}\right).\end{aligned} \tag{S1.2}$$

Here $\phi_{a\alpha}$ is the number of contacts between a person in age group $a$ with people in age group $\alpha$, $\beta$ is the probability of infection for a susceptible person who has contact with an infectious person, and $\sigma_a$ is the relative susceptibility of people in age group $a$. The relative susceptibility incorporates the potential for people to have some immunity to the current seasonal influenza strain due to exposure to a similar virus in previous influenza season. The total population size is $N$:

$$\begin{aligned}N_a = {} & S_{\mathrm{LU}a} + E_{\mathrm{LU}a} + I_{\mathrm{LU}a} + R_{\mathrm{LU}a} + S_{\mathrm{HU}a} + E_{\mathrm{HU}a} + I_{\mathrm{HU}a} + R_{\mathrm{HU}a} \\ & + S_{\mathrm{LV}a} + E_{\mathrm{LV}a} + I_{\mathrm{LV}a} + R_{\mathrm{LV}a} + S_{\mathrm{HV}a} + E_{\mathrm{HV}a} + I_{\mathrm{HV}a} + R_{\mathrm{HV}a},\end{aligned} \tag{S1.3}$$

$$N = \sum_a N_a. \tag{S1.4}$$

The demographic effects of aging, birth, and death by causes not related to influenza are not included because we only model one influenza season, where these demographic effects are small.

Numerical solution of the model differential equations was done using the LSODA routine [5].

### S1.1.2 Parameter Values

The model epidemiological parameters and their distributions are listed in Table 1 in the main text. We parametrized the contact matrix ($\phi_{a\alpha}$), which describes the number of potentially transmitting contacts per day between a person in age group $a$ and people in age group $\alpha$, as in Medlock & Galvani [7], using survey-based data [8].

We assumed that the empirical case mortality ($d_a$) was to people with the same proportion of the risk groups as the overall population and, of course, to all unvaccinated people. The case mortality for low-risk, unvaccinated people is then

$$d_{\mathrm{LU}a} = \frac{d_a}{(1 - P_{\mathrm{H}a}) + d_{\mathrm{HL}}P_{\mathrm{H}a}}, \tag{S1.5}$$

where $d_{\mathrm{HL}}$ is the relative increase of the risk of death for high-risk people. In terms of the model parameters recovery rate ($\gamma_a$) and death rate for low-risk, unvaccinated people ($\nu_{\mathrm{LU}a}$), the case mortality for low-risk, unvacinated people is

$$d_{\mathrm{LU}a} = \frac{\nu_{\mathrm{LU}a}}{\gamma_a + \nu_{\mathrm{LU}a}}. \tag{S1.6}$$

Accordinly, death rate for the low risk, unvaccinated people,

$$\nu_{\mathrm{LU}a} = \gamma_a \frac{d_{\mathrm{LU}a}}{1 - d_{\mathrm{LU}a}}. \tag{S1.7}$$

The case mortality for low-risk, vaccinated people is reduced from Eq. S1.7 by the vaccine efficacy against death ($\delta_a$), giving

$$\nu_{\mathrm{LV}a} = \gamma_a \frac{(1-\delta_a) d_{\mathrm{LU}a}}{1 - (1-\delta_a) d_{\mathrm{LU}a}}. \tag{S1.8}$$

The death rates of high-risk people are

$$\nu_{\mathrm{HU}a} = \gamma_a \frac{d_{\mathrm{HL}} d_{\mathrm{LU}a}}{1 - d_{\mathrm{HL}} d_{\mathrm{LU}a}}, \tag{S1.9}$$

$$\nu_{\mathrm{HV}a} = \gamma_a \frac{d_{\mathrm{HL}} (1-\delta_a) d_{\mathrm{LU}a}}{1 - d_{\mathrm{HL}} (1-\delta_a) d_{\mathrm{LU}a}}. \tag{S1.10}$$

Note here that we have assumed that the vaccine efficacy against death reduces the case mortality by the same relative amount in both low-risk and high-risk people.

Similarly, we took the empirical case hospitalization ($c_a$) to be to people in the same proportion of the risk groups as the overall population. Then the model case hospitalization for low-risk people ($c_{\mathrm{L}a}$) is

$$c_{\mathrm{L}a} = \frac{c_a}{(1 - P_{\mathrm{H}a}) + c_{\mathrm{HL}} P_{\mathrm{H}a}}, \tag{S1.11}$$

where $c_{\mathrm{HL}}$ is the relative increase in the risk of hospitalization for high-risk people.

We parametrized the contact matrix, $\phi_{a\alpha}$, using the results of a study in eight countries in Europe that asked respondents to keep a diary of their contacts [8]. The study estimated the number of contacts per respondent by age of the respondent and age of the contact, where the age groups were in five-year blocks, ages $0-4$, $5-9$, $\ldots$, $65-69$, and $70+$. These data reveal

considerable contact within age groups, as well as significant contact between children and adults the age of their parents [8].

Letting $c_{a\alpha}$ be the number of contacts per person in age group a with people in age group $a$, the elements of the contact matrix are given by dividing $c_{a\alpha}$ by the proportion of the population in age group $a$:

$$\hat{\phi}_{a\alpha} = \frac{c_{a\alpha}}{N_\alpha/N} \tag{S1.12}$$

For each country, we used $c_{a\alpha}$ and census data included in the study for $N_\alpha$ to give $\hat{\phi}_{a\alpha}$. We ensured that the number of contacts between age groups was symmetric,

$$N_a c_{a\alpha} = N_\alpha c_{\alpha a} \rightarrow \phi_{a\alpha} = \phi_{\alpha a}, \tag{S1.13}$$

by using the contact matrix

$$\phi_{a\alpha} = \frac{\hat{\phi}_{a\alpha} + p\hat{h}i_{\alpha a}}{2}. \tag{S1.14}$$

This calculation provided a contact matrix for each country: we then took the mean over the eight countries as the contact matrix for our model. To convert between the study's 15 age groups, the contact rates from the study's age group $0-4$ were assumed to apply equally to our age groups 0 and $1-4$: $\phi_{0\alpha} = \phi_{1\alpha}$ and $\phi_{a0} = \phi_{a1}$. Likewise, the contact rates from the study's age group 70+ were assumed to apply equally to our age groups $70-74$ and 75+.

The probability of transmission given a suitable contact ($\beta$), was then chosen so that the model's basic reproductive number (in the absence of vaccination) had a proscribed value (see Table 1, Main text).

### S1.1.3 Reproductive Number

The basic reproductive number ($R_0$) of model (S1.1) was calculated using the next-generation matrix [3, 7, 15]. No closed form expression is available for $R_0$ for model (S1.1): rather, it is given by the leading eigenvalue of a matrix that depends on the model parameters.

Consider the case when no one in the population has been exposed to the

pathogen and there is no vaccination. Define the sub-matrices

$$\mathbf{F}_{\mathrm{L}} = [F_{\mathrm{L}a\alpha}] = \left[\beta\sigma_a \frac{(1-P_{\mathrm{H}a})N_a}{N}\phi_{a\alpha}\right], \tag{S1.15}$$

$$\mathbf{F}_{\mathrm{H}} = [F_{\mathrm{H}a\alpha}] = \left[\beta\sigma_a \frac{P_{\mathrm{H}a}N_a}{N}\phi_{a\alpha}\right], \tag{S1.16}$$

$$\mathbf{V}_{\mathrm{L}} = [V_{\mathrm{L}a\alpha}] = [\gamma_a + \nu_{\mathrm{LU}a}\delta_{a\alpha}], \tag{S1.17}$$

$$\mathbf{V}_{\mathrm{H}} = [V_{\mathrm{H}a\alpha}] = [\gamma_a + \nu_{\mathrm{HU}a}\delta_{a\alpha}]. \tag{S1.18}$$

Here, $\delta_{a\alpha}$ is the Dirac delta:

$$\delta_{a\alpha} = \begin{cases} 1, & \text{if } a = \alpha, \\ 0, & \text{otherwise.} \end{cases} \tag{S1.19}$$

Now define the matrices

$$\mathbf{F} = \begin{bmatrix} \mathbf{F}_{\mathrm{L}} & \mathbf{0} \\ \mathbf{0} & \mathbf{F}_{\mathrm{H}} \end{bmatrix}, \tag{S1.20}$$

$$\mathbf{V} = \begin{bmatrix} \mathbf{V}_{\mathrm{L}} & \mathbf{0} \\ \mathbf{0} & \mathbf{V}_{\mathrm{H}} \end{bmatrix}. \tag{S1.21}$$

Finally,

$$R_0 = \rho\left(\mathbf{F}\mathbf{V}^{-1}\right), \tag{S1.22}$$

where $\rho(\mathbf{M})$ is the largest magnitude of the eigenvalues of the matrix $\mathbf{M}$.

This calculation of $R_0$ is easily extended to include a population with both unvaccinated and vaccinated people.

In the next-generation matrix ($\mathbf{M}$), every element $\mathbf{M}_{ij}$ is the expected number of infected individuals in the age group $i$ that would arise from a primary infected individual in age-group $j$ in a susceptible population. To determine the contribution of a given age group ($k$) to disease transmission within the entire population, we proceeded as follows:

1. We build the next-generation matrix ($\mathbf{M}$) for the whole population.

2. We find the eigenvector ($\mathbf{v}$) associated with the largest eigenvalue ($R_0$) of $\mathbf{M}$.

3. We split $\mathbf{v}$ into $\mathbf{v} = \mathbf{v}_k + \mathbf{v}_o$, where $\mathbf{v}_k$ is non-zero only in age group $k$ (for both risk groups) and $\mathbf{v}_o$ is non-zero in the other age groups.

4. The number of new infected individuals in each age group that arise from a primary infection case in age group $k$ is

$$\mathbf{n}_k = \mathbf{M}\mathbf{v}_k/\|\mathbf{v}_k\|. \tag{S1.23}$$

Likewise, the number of new infections in each age group that arise from an infection in the other age groups is

$$\mathbf{n}_o = \mathbf{M}\mathbf{v}_o/\|\mathbf{v}_o\|. \tag{S1.24}$$

Here

$$\|\mathbf{v}\| = \sum_i |v_i|. \tag{S1.25}$$

To compute the number of new infections in age group $k$ caused by an infected individual in age group $k$ (here denoted the within-group reproductive number of age group $k$), we summed the new infections in age group $k$ in $\mathbf{n}_k$:

$$R_{kk} = \mathbf{e}_k \cdot \mathbf{n}_k, \tag{S1.26}$$

where $\mathbf{e}_k$ is 1 in age group $k$ (for both risk groups) and 0 everywhere else, and $\cdot$ is the standard dot product. To compute the number of new infections in other age groups caused by an infected individual in age group $k$ (here denoted the between-group reproductive number of age group $k$), we summed the new infections in other age groups in $\mathbf{n}_k$:

$$R_{ko} = (\mathbf{1} - \mathbf{e}_k) \cdot \mathbf{n}_k, \tag{S1.27}$$

where $\mathbf{1}$ is the vector of all ones. Similarly for infections from the other age groups to age group $k$

$$R_{ok} = \mathbf{e}_k \cdot \mathbf{n}_o, \tag{S1.28}$$

and for infections from the other age groups to the other age groups

$$R_{oo} = (\mathbf{1} - \mathbf{e}_k) \cdot \mathbf{n}_o. \tag{S1.29}$$

Note that these reproduction numbers for age groups include both high- and low-risk groups.

### S1.1.4 Optimal Vaccine Allocation

We denote by $v$ the total number of vaccine doses available. Let $p_{\mathrm{L}a_{\mathrm{L}}}$ be the proportion of low-risk people in age group $a_{\mathrm{L}}$ who are vaccinated and $p_{\mathrm{H}a_{\mathrm{H}}}$ be the proportion of high-risk people in age group $a_{\mathrm{H}}$ who are vaccinated; these are the control variables. New age groups $a_{\mathrm{L}} = 1, 2, \ldots, A_{\mathrm{L}}$ and $a_{\mathrm{H}} = 1, 2, \ldots, A_{\mathrm{H}}$, have been introduced to allow for vaccine policies that have different age groups than those in epidemic model (S1.1) itself. In particular, we will consider finding the best way to distribute vaccine to the 5 low-risk age groups ($A_{\mathrm{L}} = 5$) 0–4, 5–17, 18–44, 45–64, and 65+ and a single group for high-risk people of all ages ($A_{\mathrm{H}} = 1$). Define the factor $G_{\mathrm{L}aa_{\mathrm{L}}}$ to be the fraction of low-risk people in model age group $a$ who are also in vaccination age group $a_{\mathrm{L}}$ and $G_{\mathrm{H}aa_{\mathrm{H}}}$ is defined similarly for high-risk people: these convert between the age groups used in epidemic model (S1.1) and those used as the basis for vaccine distribution. For our age groups, these are

$$\mathbf{G}_{\mathrm{L}} = \begin{bmatrix} 0.5 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0.6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0.4 & 1 & 1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 \end{bmatrix}, \quad \text{(S1.30)}$$

with 0.5 in the first entry arising due to the vaccine not being used in children under 6 months old [1] (i.e. assuming half of the under-1-year age group is under 6 months old) and 0.6 and 0.4 arising because we assume that 60% of 15–19 year-olds are under 18 and 40% are 18 or older, and

$$\mathbf{G}_{\mathrm{H}} = \begin{bmatrix} 0.5 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix}, \quad \text{(S1.31)}$$

since high-risk people of all ages are combined into one vaccination group. Then, given the proportions vaccinated in the vaccination age-risk groups, $p_{\mathbf{L}a_{\mathrm{L}}}$ and $p_{\mathbf{H}a_{\mathrm{H}}}$, the proportions vaccinated in the epidemic model's age-risk groups are

$$q_{\mathrm{L}a} = \sum_{a_{\mathrm{L}}} G_{\mathrm{L}aa_{\mathrm{L}}} p_{\mathrm{L}a_{\mathrm{L}}}, \quad \text{(S1.32)}$$

$$q_{\mathrm{H}a} = \sum_{a_{\mathrm{H}}} G_{\mathrm{H}aa_{\mathrm{H}}} p_{\mathrm{H}a_{\mathrm{H}}}. \quad \text{(S1.33)}$$

The epidemic is then initiated with the specified proportion of each age-risk group vaccinated, with one infectious person in each age-risk group, and the

remaining population susceptible. The initial conditions for epidemic model (S1.1) are then

$$\begin{aligned}
S_{\mathrm{LU}a}(0) &= (1-q_{\mathrm{L}a})\left[(1-P_{\mathrm{H}a})N_a - 1\right], \\
S_{\mathrm{HU}a}(0) &= (1-q_{\mathrm{H}a})\left(P_{\mathrm{H}a}N_a - 1\right), \\
S_{\mathrm{LV}a}(0) &= q_{\mathrm{L}a}\left[(1-P_{\mathrm{H}a})N_a - 1\right], \\
S_{\mathrm{HV}a}(0) &= q_{\mathrm{H}a}\left(P_{\mathrm{H}a}N_a - 1\right), \\
E_{\mathrm{LU}a}(0) &= 0, \\
E_{\mathrm{HU}a}(0) &= 0, \\
E_{\mathrm{LV}a}(0) &= 0, \\
E_{\mathrm{HV}a}(0) &= 0, \\
I_{\mathrm{LU}a}(0) &= 1-q_{\mathrm{L}a}, \\
I_{\mathrm{HU}a}(0) &= 1-q_{\mathrm{H}a}, \\
I_{\mathrm{LV}a}(0) &= q_{\mathrm{L}a}, \\
I_{\mathrm{HV}a}(0) &= q_{\mathrm{H}a}, \\
R_{\mathrm{LU}a}(0) &= 0, \\
R_{\mathrm{HU}a}(0) &= 0, \\
R_{\mathrm{LV}a}(0) &= 0, \\
R_{\mathrm{HV}a}(0) &= 0,
\end{aligned} \tag{S1.34}$$

where $N_a$ is the number of people of age $a$ (from the estimated 2010 US population [14]) and $P_{\mathrm{H}a}$ is the proportion of age group $a$ who are high risk. (The initial infectious person in each age-risk group is divided between the vaccinated and unvaccinated groups in proportion to the vaccination in that age-risk group so that the initial conditions are consistent across all vaccination levels $0 \leq q_{ra} \leq 1$.)

The cumulative number of infections at time $T$ is

$$N_{\mathrm{ILU}a}(T) = N_{\mathrm{LU}a}(0) - S_{\mathrm{LU}a}(T), \tag{S1.35}$$
$$N_{\mathrm{IHU}a}(T) = N_{\mathrm{HU}a}(0) - S_{\mathrm{HU}a}(T), \tag{S1.36}$$
$$N_{\mathrm{ILV}a}(T) = N_{\mathrm{LV}a}(0) - S_{\mathrm{LV}a}(T), \tag{S1.37}$$
$$N_{\mathrm{IHV}a}(T) = N_{\mathrm{HV}a}(0) - S_{\mathrm{HV}a}(T), \tag{S1.38}$$

for unvaccinated low-risk, unvaccinated high-risk, vaccinated low-risk, and

vaccinated high-risk people, respectively. Here

$$N_{\mathrm{LU}a} = S_{\mathrm{LU}a} + E_{\mathrm{LU}a} + I_{\mathrm{LU}a} + R_{\mathrm{LU}a}, \tag{S1.39}$$
$$N_{\mathrm{HU}a} = S_{\mathrm{HU}a} + E_{\mathrm{HU}a} + I_{\mathrm{HU}a} + R_{\mathrm{HU}a}, \tag{S1.40}$$
$$N_{\mathrm{LV}a} = S_{\mathrm{LV}a} + E_{\mathrm{LV}a} + I_{\mathrm{LV}a} + R_{\mathrm{LV}a}, \ \textit{and} \tag{S1.41}$$
$$N_{\mathrm{HV}a} = S_{\mathrm{HV}a} + E_{\mathrm{HV}a} + I_{\mathrm{HV}a} + R_{\mathrm{HV}a}, \tag{S1.42}$$

are the numbers of people summed over infection status. The cumulative number of deaths is

$$N_{\mathrm{D}a}(T) = N_a(0) - N_a(T), \tag{S1.43}$$

where

$$N_a = N_{\mathrm{LU}a} + N_{\mathrm{HU}a} + N_{\mathrm{LV}a} + N_{\mathrm{HV}a} \tag{S1.44}$$

is the total number of people in age group $a$. We will minimize, at the end time $T$, the objective function that is either total infections, total deaths, total hospitalizations, total years of life loss, or contingent valuation. Total infections are given by

$$I(T) = \sum_a \left[ N_{\mathrm{IL}a}(T) + N_{\mathrm{IH}a}(T) \right], \tag{S1.45}$$

where

$$N_{\mathrm{IL}a} = N_{\mathrm{ILU}a} + N_{\mathrm{ILV}a}, \ \textit{and} \tag{S1.46}$$
$$N_{\mathrm{IH}a} = N_{\mathrm{IHU}a} + N_{\mathrm{IHV}a}, \tag{S1.47}$$

are the numbers of infections in age group $a$ to low-risk and high-risk people, respectively. Total deaths are given by

$$D(T) = \sum_a N_{\mathrm{D}a}(T). \tag{S1.48}$$

Total hospitalizations are given by

$$H(T) = \sum_a \left[ h_{\mathrm{L}a} N_{\mathrm{IL}a}(T) + h_{\mathrm{H}a} N_{\mathrm{IH}a}(T) \right], \tag{S1.49}$$

where $h_{\mathrm{L}a}$ and $h_{\mathrm{H}a}$ are the case hospitalizations for low-risk and high-risk people in age group $a$. Note that here we have assumed that the risk of hospitalization is independent of vaccination status. Total years of life lost are given by

$$Y(T) = \sum_a \mathbf{e} N_{\mathrm{D}a}(T), \tag{S1.50}$$

where $e_a$ is the expectation of life for age group $a$, i.e. the expected number of years of life remaining for a person in age group $a$ [11]. The 2006 US expectation of life [10] is in 1-year age groups, which we reduced to the 17 model age groups by taking sums over the age groups weighted according to the 2010 population age structure. Contingent valuation is given by

$$C(T) = \sum_a \mathbf{c} N_{\mathrm{D}a}(T), \tag{S1.51}$$

where $\mathrm{c}_a$ is the relative value of an individual in age group $a$. Cropper *et al.* [2] use

$$\mathrm{c}_a = a^{\omega-1} \exp(-\phi a^{\omega}), \tag{S1.52}$$

and estimate $\omega = 2.6$ and $\phi = 0.000104$ from survey data [4, 6]. As for the years of life loss, we reduced the contingent valuation from 1-year age groups to the 17 model age groups by using sums weighted according to the 2010 US population age structure.

Given the starting time ($t = 0$) and the end time ($t = T$), we found the $p_{\mathrm{L}a_{\mathrm{L}}}$ and $p_{\mathrm{H}a_{\mathrm{H}}}$ that minimize the objective function, subject to the feasibility conditions

$$0 \leq p_{\mathrm{L}a_{\mathrm{L}}} \leq 1, \tag{S1.53}$$

$$0 \leq p_{\mathrm{H}a_{\mathrm{H}}} \leq 1, \ \textit{and} \tag{S1.54}$$

$$\sum_a \left[ q_{\mathrm{L}a} S_{\mathrm{LU}a} + q_{\mathrm{H}a} S_{\mathrm{HU}a} \right] \leq v, \tag{S1.55}$$

the latter of which ensures that the number of vaccines used is below the number available; as well as subject to the initial conditions (S1.34) at $t = 0$, and to the differential equations (S1.1) on $0 < t \leq T$.

For a given vaccine distribution schedule, the optimal vaccine allocations were calculated numerically using the constrained optimization by linear approximation (COBYLA) algorithm [12], run three times with random initial vaccination levels. We took the optimum to be the result with the smallest value of the objective function among these three runs.

## S1.2 Sensitivity Index

To compute the sensitivity index, we first computed optimal vaccine allocation for 5000 sets of independently sampled parameter values. Simulating this

sampled set was computationally expensive. Therefore, for computational efficiency, we fitted the input parameters and output variables of our model to a second-order regression model (with regression coefficient $R^2$ larger than 0.65) that we used to compute the first order sensitivity index[13]. The sensitivity index obtained via the regression model provides a good approximation of the the sensitivity index of the original model [9].

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